CLINICOPATHOLOGICAL CORRELATIONS IN UNILATERAL GLAUCOMA

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THE presence of glaucoma in one eye should alert the ophthalmologist to the significance of its etiology and differential diagnosis. Certain types of glaucoma are characteristically unilateral and may be classified as secondary open-angle and angle-closure types. Further subclassification of the open-angle type may delineate those cases caused by the presence of cells or debris in the angle and those due to damaged outflow channels. Table I lists the open-angle unilateral glaucomas caused by cells or debris in the angle, and Table II lists the open-angle unilateral glaucomas caused by damaged outflow channels.

The eye following contusion may show a variety of problems; among them is hyphema or blood in the anterior chamber angle. The presence of blood or hemosiderin-laden macrophages may mechanically block the anterior chamber angle and lead to a secondary open-angle glaucoma. Unilateral glaucoma due to intraocular inflammation is often encountered when glaucoma is observed during the course of a recognized uveitis. However, less obvious causes exist and the diagnosis can only be made after a careful examination of the eye. One such condition is Fuchs' heterochromic iridocyclitis,[1] a condition in which a secondary open-angle glaucoma develops almost invariably in one eye although it has been reported bilaterally. Associated with the glaucoma is a lowgrade iridocyclitis and the eventual development of cataract. The condition is often associated with a white quiet eye and the heterochromia which eventually is certainly one of the hallmarks of this condition. No peripheral anterior

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TABLE I. UNILATERAL GLAUCOMAS (SECONDARY TYPE) OPEN ANGLE

Cells or debris in the angle
1) Hyphema
2) Uveitis
a) Iridocyclitis (e.g., Fuchs' heterochromic)
b) Glaucomatocyclitic crisis
3) Phacolytic glaucoma
4) Following lens rupture
5) Hemolytic glaucoma
6) Pigmentary glaucoma
7) Malignant melanoma
8) Pseudoexfoliation of the lens capsule (exfoliation syndrome)
9) Metastatic carcinoma

synechiae or posterior synechiae are present but, characteristically, fine new blood vessels develop on the surface of the ciliary band, on the scleral spur, and on the meshwork. These vessels may be easily overlooked without careful examination. Histopathologic examination of the eye in such a condition reveals chronic granulomatous inflammation within the iris, ciliary body, and trabecular meshwork. Inflammatory membranes have been reported on the anterior surface of the iris and face of the ciliary body. The histopathological counterpart of the fine neovascularization seen in the angle may be observed on the face of the iris as well. The iris stroma and pigment epithelium are atrophic.

Phacolytic glaucoma as delineated by Flocks, Littwin, and Zimmerman[2] is a type of secondary open-angle glaucoma associated with acute glaucoma in which the intraocular tension may be very high. A hypermature cataract with aqueous flare and cells, often in clumps, are associated, and on occasion a hypopyon may be present. There is an associated recession of the anterior chamber angle in approximately 25% of eyes enucleated for phacolytic glaucoma. Cytologic examination of aqueous aspirates revealed macrophages filled with lens-derived material, and histopathologic examination of enucleated eyes shows a hypermature cataract with loss of cortical material and an open anterior chamber angle with macrophages laden with lens material. Similar lens-material-filled macrophages are present upon and within the iris and within the trabecular meshwork.

Pseudoexfoliation of the lens capsule or, as Sugar[3] has termed the condition, "the exfoliation syndrome," is a common disorder with a cosmopolitan distribution. There is some predilection for Scandinavians

TABLE II. UNILATERAL GLAUCOMAS (SECONDARY TYPE) OPEN ANGLE

Damaged outflow channels
1) Hemosiderosis (or siderosis) bulbi
2) Trauma
   a) Direct effect
   b) Postcontusion angle deformity
      i. with endothelialization
3) Alpha-chymotrypsin induced
4) Steroid induced
5) Postinflammatory
6) Associated with extraocular disease, e.g., cavernous sinus thrombosis

although we have seen the condition in nearly all racial groups. The exfoliation syndrome is most likely an inherited disorder, possibly inherited as an autosomal dominant with incomplete penetrance and invariable expressivity. It occurs in individuals between the ages of 60 and 80 years, and is unilateral in 50% of the cases with an associated open-angle glaucoma in 70% of patients. Clinically, the exfoliated material is present on the pupillary ruff of the iris, anterior iris surface, in the anterior chamber angle, and in a characteristic distribution on the anterior lens capsule. The anterior lens capsule shows a typical central disc surrounded by a clear zone, which is in turn surrounded by a peripheral granular area. Gonioscopy reveals the deposition of pigment (from the iris pigment epithelium) in the meshwork. There is increased transillumination of the iris near the pupil. Histopathologic examination shows the typical eosinophilic material on the anterior surface of the lens, on the vitreous face and zonular fibers, upon and within the anterior and posterior surfaces of the iris and ciliary body, in the anterior chamber angle and trabecular meshwork, and around conjunctival blood vessels.

Metastatic carcinoma to the iris[4] is unusual but may cause unilateral open-angle glaucoma. The hallmark of metastatic carcinoma to the iris is the presence on the iris surface of translucent, gelatinous nodules which may extend to the angle and occlude the meshwork. Occasionally iritis is present, rarely hypopyon. In some instances rubeosis iridis and iris atrophy are present. Rarely, a patient with carcinoma metastatic to the iris presents with a hyphema. Cytologic examination of aqueous aspirates may reveal the presence of carcinoma cells. Fluorescein angiography of the iris may show a vascularized lesion which displays leakage in the late phase. Histopathologic examination reveals infiltration of the iris and angle structures by tumor cells.

The second group of open-angle unilateral glaucomas is due to damage to the outflow channels. One such condition is hemosiderosis bulbi[5] secondary to intraocular hemorrhage or siderosis bulbi due to the retention of an iron-containing foreign body. In both conditions ionized iron may spread to all ocular tissues, but is mainly deposited in epithelial cells. Heterochromia and unilateral glaucoma may develop with an associated loss of vision from a toxic affect on the retina. Histopathological examination reveals deposition of iron in the corneal epithelium, iris pigment epithelium, iris dilator and sphincter muscles, both pigmented and non-pigmented ciliary epithelium, lens epithelium, trabecular meshwork, retinal pigment epithelium, and within the sensory retina. The latter may lead to retinal degeneration and gliosis. Trauma may produce a secondary open-angle glaucoma by a direct effect or a postcontusion angle deformity.[6] The direct effect of trauma on the anterior chamber angle is scarring of the meshwork while postcontusion angle deformity or angle recession is caused by laceration of the anterior face of the ciliary body with posterior displacement of the iris root and pars plicata of the ciliary body except for the longitudinal ciliary muscle. Open-angle glaucoma develops in approximately 6% of eyes with angle recession, although, with more and more of the angle recessed, glaucoma occurs with a higher frequency. Posttraumatic hyphema is associated with angle recession in 40 to 60% of cases. The glaucoma is due to sclerosis and secondary open-angle glaucoma, endothelialization of the anterior chamber, or secondary angle closure.

The second broad group of secondary unilateral glaucomas is due to angle closure and is invariably associated with peripheral anterior synechiae. These causes are listed in Table III. The most common cause of peripheral anterior synechiae is rubeosis iridis. Rubeosis iridis leads to neovascular glaucoma if the new blood vessels with their attendant fibrous matrix forming on the iris surface extend into the angle and produce angle closure. Such neovascularization of the iris can be caused by a variety of conditions:

1) Vascular (nonocular) such as giant cell arteritis, aortic arch syndrome, carotid occlusive disease, carotid ligation, and carotid cavernous fistula (ocular: central retinal vein or artery occlusion)

2) Inflammatory: uveitis, endophthalmitis, following radiotherapy

3) Neoplastic: uveal malignant melanoma, retinoblastoma, metastatic carcinoma

TABLE III. UNILATERAL GLAUCOMAS (SECONDARY TYPE) ANGLE CLOSURE

Peripheral anterior synechiae
1) With rubeosis iridis
2) Without rubeosis iridis
a) Chronic angle closure glaucoma
3) Lens induced
a) Swollen lens
b) Dislocated lens
4) Flat chamber
5) Essential iris atrophy
6) Chandler's syndrome
7) Iris nevus syndrome
8) Epithelial invasion of the anterior chamber
9) Endothelialization of the anterior chamber
10) Malignant melanoma
11) Juvenile xanthogranuloma

4) Embryonal medulloepithelioma of the ciliary body

5) Retinal diseases: diabetes mellitus, retinal detachment, Coats' disease, Leber's disease, sickle cell retinopathy, retinopathy of prematurity (retrolental fibroplasia), Eales' disease, persistent hyperplastic primary vitreous, and Norrie's disease

The iris nevus syndrome[7] is a condition in which secondary open-angle glaucoma occurs unilaterally. Clinically, there are iris nodules with obliteration of the crypts and folds and heterochromia. Peripheral anterior synechiae may be caused by the diffuse anterior surface iris nevi and endothelialization of the anterior chamber angle may develop.

Epithelial invasion of the anterior chamber may occur following injury or surgery and may result in secondary angle-closure glaucoma. Epithelium[8] within the eye may be classified as 1) epithelial downgrowth (epithelialization), 2) serous cyst of the iris, 3) solid or pearl tumor of the iris, 4) epithelial implantation membrane. Typical epithelialization or epithelial downgrowth following trauma or surgery is characterized by the presence of a thin, translucent, grey avascular membrane on the posterior surface of the cornea, in the anterior chamber angle, on the anterior surface of the iris, and on the vitreous face. As the epithelium extends on the posterior surface of the cornea, it displays a scalloped, slightly ridged advancing edge. The differential diagnosis is corneal scar with a bevelled incision, stripped Descemet's membrane, retained lens-capsule remnants, endothelialization, and rarely stromal overgrowth. Histopathologic examination of specimens with epithelial downgrowth reveal by serial sectioning a site of entry of the epithelium, usually at an area of poorly apposed

wound edges. Epithelium may then be seen to advance along the posterior surface of the cornea to the anterior chamber angle and upon the anterior surface of the iris to the vitreous face. Often part of the iris is incarcerated in the wound. Many modalities of treatment have been offered for this condition, including radical anterior segment reconstruction. Serous cysts of the iris are characterized by translucent cysts which develop within the anterior chamber, usually attached to the wound edge, although they may be present at a site removed from the area of surgery or trauma. The cysts are translucent and contain a pseudohypopyon of cells in the inferior portion. As the cysts enlarge, glaucoma may develop. Care must be exercised in removing these cysts because rupture may transform a simple cyst into a more ominous epithelialization of the anterior chamber. Histopathologic examination of these cysts reveal their origin in conjunctival epithelium. The pearl tumor is a variation on the same theme, but the cyst is derived from keratinizing epithelium from the skin. The fourth type of epithelial invasion is due to implantation membranes which result when epithelium, either conjunctiva or skin, is deposited upon the iris surface following trauma or during surgery. Histopathologic examination of two such cases revealed conjunctival epithelium in one instance and, in the second, keratinized stratified squamous epithelium. Curiously, in the second case the skin epithelium showed *Pityrosprum ovale,* indicating its origin from eyelid tissue, probably from the canthotomy performed at the time of surgery.

Endothelialization[7] of anterior chamber is a well-recognized condition which may occur in association with postcontusion-angle deformity, rubeosis iridis, iris nevus syndrome, and essential iris atrophy. Histopathologic examination of these eyes reveals in postcontusion-angle deformity the extension of endothelium and newly formed Descemet's membrane over the anterior chamber angle. This may account for the presence of a glasslike membrane on the surface of the meshwork in such angles following trauma. We have been struck by the common association of rubeosis iridis and endothelialization of the anterior chamber. At the site of the pseudoangle where the iris is apposed to the cornea, endothelium and Descemet's membrane extend onto the anterior iris surface. As previously mentioned, the iris nevus syndrome is associated with endothelialization.

As a separate group, malignant melanoma is associated with a variety of glaucoma mechanisms, and these are enumerated in Table IV.[9] In the

TABLE IV. MALIGNANT MELANOMA GLAUCOMA MECHANISMS[9]

Open angle
1) Seeding of the anterior chamber
2) Infiltration of the angle
3) Necrosis of tumor with phagocytosis (melanomalytic)
Angle closure
1) Rubeosis iridis
2) Compression of the anterior segment
3) Diffuse iris nevus or melanoma

open-angle category, malignant melanomas may produce glaucoma by seeding of the anterior chamber, infiltration of the angle, or necrosis of the tumor with phagocytosis (melanomalytic glaucoma). Malignant melanoma may produce angle closure by virtue of rubeosis iridis, compression of the anterior segment, or in association with diffuse iris nevus or diffuse melanoma. In malignant melanoma, tumor cells may seed the anterior chamber and mechanically block the anterior chamber angle. Similar seeding of the anterior chamber may occur in association with metastatic carcinoma or in association with juvenile xanthogranuloma. Ring melanomas arising from the root of the iris and ciliary body for 360° may directly invade the anterior chamber angle to block mechanically the outflow of aqueous and produce an open-angle type of glaucoma. Yanoff has reported on malanomalytic glaucoma from partial or complete necrosis of ciliary body or iris root malignant melanomas.[9] Melanin pigment is liberated by the necrotic cells. The liberated melanin is then phagocytosed by macrophages which are carried to the anterior chamber angle and produce an obstruction and consequent open-angle glaucoma. Malignant melanomas of the uveal tract can produce angle closure by formation of rubeosis iridis. On occasion, large uveal melanomas arising posteriorly may produce total retinal detachment and, with or without associated hemorrhage, may combine to displace the lens-iris diaphragm anteriorly and compress the anterior segment. Finally, diffuse melanomas of the iris, such as the tapioca melanoma, may produce extensive invasion of the iris and eventual closure of the angle.

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